Narrative Review Article

Ehlers-Danlos Syndrome: Using AI to Bridge the Diagnostic Gap

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ABSTRACT

Ehlers-Danlos syndrome (EDS) is a primarily genetic disorder, typically resulting from mutations in collagen-encoding genes. There are thirteen varieties of EDS, each presenting different symptoms and characteristics. Common symptoms include skin elasticity, hypermobility, abnormal scar formation, and bruising. EDS is a complex syndrome and lacks a definite diagnosis method, leading to frequent misdiagnosis, delayed treatment or management, and frequent feelings of resentment among patients. While there is currently no definite diagnosis system, artificial intelligence (AI) is being evaluated to aid in diagnosis, using methods such as AI-based video goniometry; Uniform Manifold Approximation and Projection (UMAP), a dimensionality reduction technique that simplifies complex data while preserving patterns; and Hierarchical Density-Based Spatial Clustering (HDBSCAN), an algorithm that utilizes clustering, grouping similar data points together without requiring predefined categories. These methods were then assessed on their feasibility, including key strengths and weaknesses such as availability and accuracy. Overall, AI interventions in diagnostics are promising innovations that can act as potent preliminary screening tools. However, the data sets that these models are trained on often lead to bias and a lack of generalizability, causing unreliability in the readings. This is further compounded by the fact that these models are "black boxes", meaning that clinicians cannot access the underlying processing route the machine uses to make a diagnosis. Therefore, while these models show promise, more clinical studies are needed to prove their feasibility in the clinical landscape.

Keywords: Ehlers-Danlos syndrome; underdiagnosis; genetics; AI; diagnosis

INTRODUCTION

Ehlers-Danlos syndrome (EDS), a musculoskeletal condition including joint hypermobility, skin extensibility, and abnormal scar formation, affects about 1 in 5000 people according to Stein *et al*. (1). Thirteen types of EDS are currently recognized, mainly involving mutations in collagen I, III, and V of the skin and the extracellular matrix (2). Due to the variation in EDS, misdiagnosis and underdiagnosis can be common. EDS patients often present with widespread pain and psychological burdens arising from said pain, making it difficult to diagnose the true condition (3). Genetic testing can help diagnose EDS patients, but some subtypes of EDS lack genetic markers to test for (4). To help remedy this limitation, artificial intelligence (AI) can serve as a tool for physicians to recognize and diagnose EDS. For example, an AI called HybridPoseN*et al*lows for the assessment of joint mobility via a smartphone app (5). Furthermore, Hierarchical Density-Based Spatial Clustering (HDBSCAN) is a technique that can be used to group patients together based on symptoms from large data sets, allowing physicians to

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have more reference patients when formulating an EDS diagnosis (6). These AI-based techniques, among others, can increase the efficiency of EDS diagnosis in patients, helping to improve EDS care in the future, though they are still nascent. This review aims to provide context on the difficulty of diagnosing EDS and critically evaluate the AI tools that may remedy this difficulty.

HISTORY AND TYPES OF EDS

Many EDS variations involve mutations in genes coding for collagens, specifically collagens I, III, and V, though some involve the extracellular matrix (ECM) and related proteins, as illustrated in Table 1 (2). Collagen is an important structural protein that supports most connective tissues, including muscles, tendons, and blood vessels (7). The type of collagen created depends on the α-chain composition, and mutations in collagen types can lead to various forms of EDS (8).

Mutations in the procollagen genes lead to Arthrochalasia EDS, characterized by hip dislocation and general joint hypermobility (9). Specifically, with the COL1A2 procollagen gene mutations, cardiac valvular EDS and the failure of heart valves can occur (10). Another procollagen gene, ADAMTS2, has mutations that lead to dermatosparaxis EDS, which is characterized by loose and fragile skin (9, 11). Classical EDS (cEDS) involves type V collagen mutations which are vital for stabilizing type I collagen in muscle, tendon, and bone (7). While most cEDS patients show type V collagen mutations, not all of them do, making diagnosis complex (12).

Type III collagen of the stretch organs, when mutated, present as vascular EDS, leading to dermal thinning and endoplasmic reticulum (ER) dilation (13). The last collagen-related EDS is Kyphoscoliotic EDS, which involves mutations in collagen folding and crosslinking proteins that results in mechanical instability, scoliosis, and arterial fragility (14).

Some EDS variations involve the ECM. Loss of function of tenascin-X, leads to classical-like EDS, unique for skin flexibility without scarring (15). Related to tenascin-X is collagen type XII, which when mutated leads to myopathic EDS, characterized by myopathy of muscles (16).

Mutations in the GAG sidechains of proteoglycans lead to Spondylodysplastic EDS, characterized by a combination of classical EDS symptoms and early aging (17). Mutations further along in the production of proteoglycans GAG chains lead to musculocontractural

Table 1. *The thirteen varieties of EDS, including common gene mutations, affected proteins, and key symptoms.*

EDS Name	Affected Proteins	Gene Mutations	Key Symptoms	References
Arthrochalasia	Type I Collagen	*COL1A1, COL1A2*	Hip dislocation, general joint mobility	9
Cardiac Valvular	Type I Collagen	*COL1A2* mRNA	Heart valve failure	10
Dermatosparaxis	Type I Collagen	*ADAMTS2*	Loose and fragile skin	9, 11
Classical	Type V Collagen	*COL5A1, COL5A2*	Joint hypermobility, skin extensibility, ease of bruising, abnormal scar formation	7
Vascular	Type III Collagen	*COL3A1*	Dermal thinning, ER dilation	13
Kyphoscoliotic	Collagen α-chains	*PLOD1*	Mechanical instability, scoliosis, arterial fragility	14
Classical Like	Tenascin-X	*TNXB*	Skin flexibility without scarring	15
Myopathic	Type XII Collagen	*COL12A1*	Muscular myopathy	16
Spondylodysplastic	ECM Proteoglycans	GAG sidechain-related genes	Classical EDS symptoms, early aging	17
Musculocontractural	ECM Proteoglycans	GAG sidechain-related genes	Craniofacial mutations, ocular defects, tissue fragility	18
Brittle cornea syndrome	PR/SET proteins	*ZNF469* and *PRDM5*	Fragile corneas	19
Periodontal	C1	*C1R* and *C1S*	Tooth loss, periodontal disease	20
Hypermobile	Unknown	Unknown	Atrophic skin, joint hypermobility, and skin looseness more than classical EDS	9

EDS, and involves craniofacial mutations, ocular defects, and tissue fragility (18). In the eyes, mutations in PR/SET proteins that regulate collagen deposition lead to Brittle cornea syndrome, characterized by fragile corneas (19). Mutations that result in abnormal function of the C1 protein lead to Periodontal EDS, characterized by tooth loss and periodontal disease (20). Yet, the last major and most common variety of EDS, hypermobile EDS (hEDS), has no known gene basis, but is characterized by atrophic skin, joint hypermobility, and skin looseness more than classical EDS (9). A summary of each variation of EDS can be found in Table 1.

MISDIAGNOSIS

With the plethora of EDS variations, it is no surprise that misdiagnosis, or the incorrect identification or failure to identify a condition (21), a prevalent issue in healthcare. In the study by Singh, Meyer, and Thomas, the rate of outpatient diagnostic errors was estimated to be 5.08%, or approximately 12 million Americans, yearly (22). Furthermore, in the 1991 Harvard study, the incidence of misdiagnosis was found to be 14% of hospital records of patients with disabling injuries caused by medical treatment (23). EDS is often misdiagnosed or undiagnosed due to the relative rarity of the disorder, lack of awareness of the syndrome among physicians, and changing diagnostic criteria (24). Furthermore, the study by Forghani, See, and McGonigle suggests that hypermobility may present a shared phenotype across a spectrum of disorders, such as inflammatory diseases, monogenic syndromes, and chromosomal abnormalities (25), further complicating the diagnosis of EDS. This underdiagnosis often results in a significant delay in the management schedule and treatment of the disorder (26).

In addition to the clinical burdens, underdiagnosing EDS often leads to negative repercussions in patients. This leaves many patients resentful due to feelings of being misbelieved and written off as having psychiatric or psychosomatic disorders (27). EDS is associated with chronic widespread physical pain, leading to psychological difficulties, often due to self-esteem issues resulting from exercise restriction, scars, keloids, fat accumulation on extremities, and other symptoms (3). Additionally, in the nationwide study by Cederlöf *et al*., EDS was associated with an increased risk of being diagnosed with Autism Spectrum Disorder, bipolar disorder, Attention-Deficit/Hyperactivity Disorder, depression, and attempted suicide (28), potentially causing medical professionals to misdiagnose EDS as one of these disorders. Thus, many patients with EDS experience a decrease in confidence in medical professionals' ability to treat them, potentially elongating the time taken to develop a treatment schedule.

Due to this mistrust, it is imperative to reevaluate how EDS patients are diagnosed. Clinicians have typically diagnosed EDS using traditional physical and phenotypic evaluations along with supplementary genetic testing if needed (29). However, issues still exist; the foremost being that hEDS currently lacks a known gene or genetic marker, making genetic testing an unreliable diagnostic tool. The primary clinical tool for assessing joint hypermobility, a trait central to hEDS diagnosis, is the Beighton Score (BS), a nine-point scoring system used to measure Generalized Joint Hypermobility (GJH) (30). It tests nine joints in the body via apposition of the thumb to the forearm, forward flexion of the trunk, and hyperextension of the elbows by 10º, hyperextension of the knees by 10º, and hyperextension of the little finger beyond 90°. A patient would be considered to have GJH if they score 4 or more points on this score. However, the BS is considered a controversial method of determining hypermobility, due to the system assessing the joints in the upper limbs primarily and disregarding many other major joints. In recent years, the development of machine learning, a type of AI that identifies patterns in data, has enabled new possibilities for earlier and more accurate diagnosis of EDS.

AI INTERVENTION

Because EDS lacks a definitive diagnostic method and relies largely on subjective clinical assessment, there is a growing need for objective, analytical diagnostic tools. AI has shown great promise as a data-driven solution to fill this gap. It can standardize evaluations to minimize human bias and objectively detect complex patterns beyond conventional evaluation (4). One promising area is AI-based video goniometry that can objectively quantify hypermobility while minimizing human error (5). This includes hybrid deep learning systems, like HybridPoseNet, that analyze videos of patients' joint movements. The system then uses special feature extraction and temporal sequence modeling to measure joint angles of patients to diagnose EDS with a 95-100% accuracy, compared to a 90% accuracy for manual measurements (5). A similar approach uses smartphone video with non-hypermobile human pose estimation libraries to extract the typical range of motion and aid in diagnosis (31). Compared to other deep learning

programs, approaches that use smartphones offer greater accessibility, especially in low-resource or remote settings. However, this accessibility may come at the cost of reduced precision and increased variability due to differences in device quality and user technique (32). Thus, these tools may be better suited for preliminary screening rather than definitive diagnosis.

Another AI solution uses machine learning to identify patients with hEDS or hypermobility spectrum disorders (HSD) and relate it to gut-brain interactions. This determines how these groups differ in psychological, autonomic, and quality-of-life outcomes, as well as demonstrating the major advances in machine learning, how it can be used to uncover phenotypic subtypes, and uncover natural groupings with multiple different factors without prior assumptions. These machine learning techniques have offered valuable insights regarding phenotypic heterogeneity and co-morbidity in EDS patients, but their application in the clinical setting is still very experimental (6). Although both clustering and classification algorithms offer a means to discern patterns from data, it does not necessarily imply causation between the variables. These developments in video phenotyping illustrate the potential of AI to increase and enhance clinical assessment in EDS patients. Methods such as Uniform Manifold Approximation and Projection (UMAP) and HDBSCAN are helpful in the detection of patterns in data, but their outputs can be influenced by parameter tuning and datasets themselves (33). Although these models help identify possible clusters, they need to be independently verified before making them applicable clinically for patient safety and reliable results.

Regarding genomics, researchers developed UMAP, a tool used to simplify large amounts of data that takes complex, high-dimensional information about symptoms and turns it into a 2-dimensional or 3-dimensional map where similar patients appear closer together. HDBSCAN is then used to identify clusters or groups of patients who share similar features (6). This analysis allows for the identification of strong genetic correlations between groups that display the same symptoms and make a data-driven analysis, revealing meaningful subtypes of hEDS/HSD that go beyond what standard diagnostic criteria can capture.

These findings become even more powerful when combined with genetic data. Scientists can integrate symptom patterns with genomic information to gain a more complete understanding of EDS. One way this is done is through whole-exome sequencing (WES) or whole-genome sequencing (WGS).These methods screen a person's DNA to look for rare or harmful changes in genes related to collagen or the ECM, which are essential for connective-tissue strength (33). By merging genetic and symptom data into the same ML system, researchers could create more accurate "genotype–phenotype" maps, linking genes to outward features or symptoms . Although EDS is varied and complex to diagnose, AI and genetic profiling bring new opportunities for diagnosis and understanding of the syndrome. As data accumulation continues, models can mature, as it provides more pictures for the model to reference actual patient results and to come to a more accurate diagnosis. These technologies have the potential to transform the diagnostic pathway for EDS, enabling earlier detection, more accurate subtype classification, personalized monitoring, and better patient outcomes.

LIMITATIONS OF ARTIFICIAL INTELLIGENCE

While AI provides great promise for the future of EDS diagnosis, there are several limitations that need to be considered. Because the syndrome is relatively rare and heterogeneous, machine learning algorithms are often trained on small or highly specific data sets, which may not accurately represent the general population. This lack of diversity in training data increases the risk of biased predictions and reduced diagnostic accuracy in broader clinical populations. Although it is possible to build this dataset diversity and variability, it is something that will take a long time to ensure that the model encompasses every variable in diagnosing EDS. Even with these advancements, the heterogeneity of EDS and variability in each individual patient may limit the readiness of AI systems for fully reliable clinical application.

Generalizability of AI systems is another limitation that must be taken into account. Algorithms designed within controlled research environments may exhibit different behavior when applied in real-life situations, where factors such as differences in imaging quality or patient demographics can affect results. In other words, models which perform exceptionally well in laboratories may not be as reliable in clinical practice unless proven otherwise.

Finally, many AI systems lack interpretability and are known as "black boxes." This means that clinicians have no way to understand why a particular diagnosis was made, which can limit their acceptance and adoption in clinical practice.

To adopt these AI and DL programs into a reliable

EDS diagnosis method, large-scale clinical trials must be done with a variety of patients and different variables such as camera angles and lighting. Additionally, some sort of architecture within these programs must be developed, so clinicians are explicitly informed on the thought process these programs use to come to the diagnostic decision.

CONCLUSION

EDS presents a uniquely complex challenge for clinical diagnosis due to symptom variability, genetic complexity, and diagnostic uncertainty. The thirteen subtypes of EDS present both distinct and overlapping manifestations, further complicating diagnosis. This is compounded in hEDS, which lacks definitive genetic markers. These limitations in diagnosis delay not only the management and treatment of the syndrome but also contribute to significant psychological and social difficulties for many patients, such as decreased trust in healthcare providers and an increased risk of comorbid mental health conditions.

While AI and machine learning offer a promising alternative for EDS diagnosis, shifting the standard from subjective clinical assessment to objective, data-driven analysis, their integration into the medical field is nascent. Techniques such as AI-based video goniometry, machine learning clustering methods like UMAP and HDBSCAN, and integrative genomic analyses demonstrate that AI can aid in EDS diagnosis. By leveraging large-scale, multidimensional datasets, these tools can help physicians make more objective decisions while reducing reliance on inconsistent clinical assessments.

However, several limitations are present in implementing AI tools in clinical settings. Future research must prioritize the development of architectures to address the "black box" nature of current algorithms, thereby ensuring that clinicians can interpret AI-generated information. Furthermore, to address the problem of bias within the datasets, future studies must be conducted that focus on large-scale clinical trials that reflect the diversity of patients with EDS across various demographics.

Ultimately, successfully integrating AI in EDS diagnosis and treatment may not only improve accuracy and efficiency, but establish a transparent, validated, and reliable framework that may restore relationships between patients and providers through accurate, early, and personalized intervention and treatment.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest related to this work.

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